Effect of luspatercept on biomarkers of erythropoiesis in patients with lower-risk myelodysplastic syndromes in the MEDALIST trial

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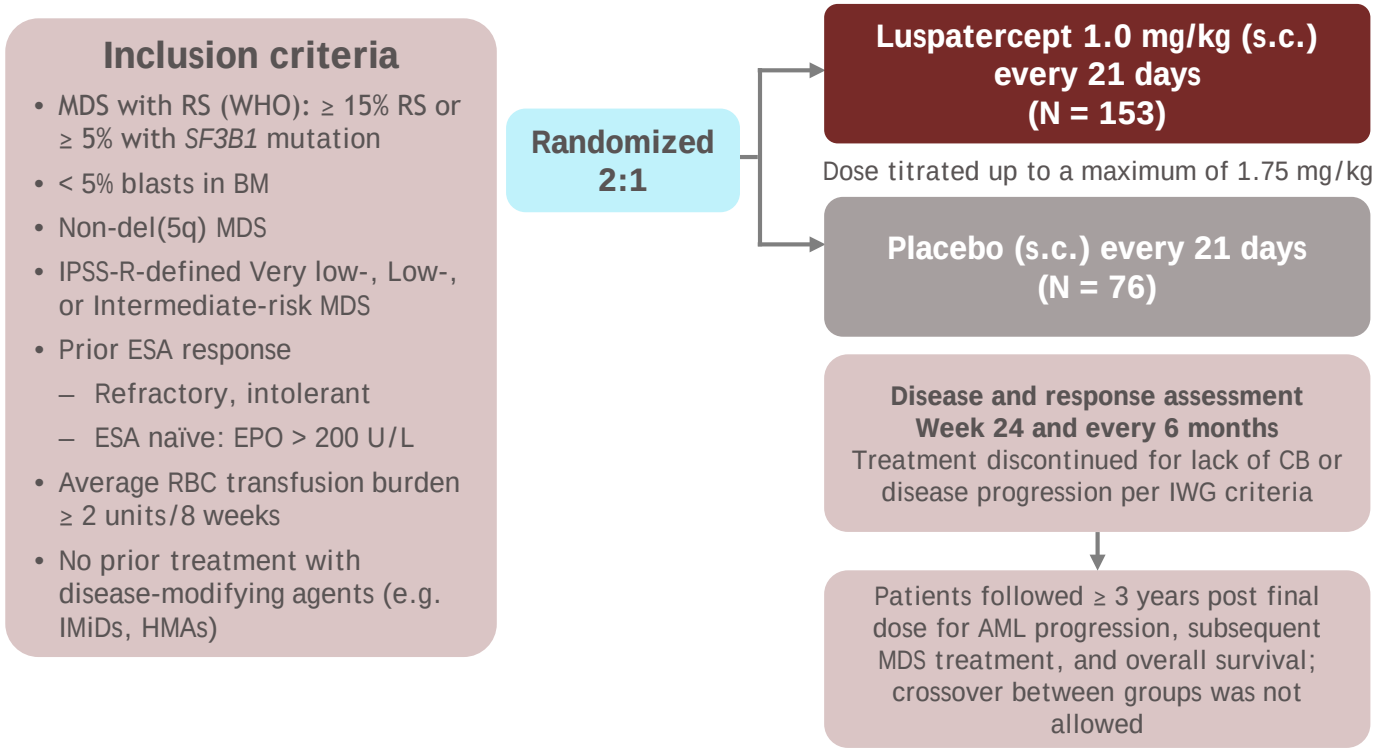
Background

- LR-MDS are characterized by ineffective erythropoiesis that leads to anemia and RBC transfusion dependence[1]
  - Treatment options are limited for patients with transfusion-dependent LR-MDS for whom ESA treatment is ineffective or is not an option[1,2]
- This analysis investigates the effect of luspatercept treatment on erythropoiesis-associated biomarkers and their relationship to CB in the primary treatment phase (Weeks 1–24) of the MEDALIST study (NCT02631070)
  - CB (defined as RBC-TI ≥ 8 weeks and/or mHI-E per IWG 2006 criteria) during Weeks 1–24 was achieved by 58.2% of patients in the luspatercept arm and 21.1% in the placebo arm ($P < 0.0001$)[3]

Figure 1. Study design of the phase 3 MEDALIST trial



AML, acute myeloid leukemia; BM, bone marrow; CB, clinical benefit; EPO, erythropoietin; ESA, erythroid-stimulating agent; HMA, hypomethylating agent; IMiD, immunomodulatory drug; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes; MDS/MPN-RS-T, myelodysplastic syndromes/myeloproliferative neoplasm with RS and thrombocytosis; mHI-E, modified hematologic improvement-erythroid; RBC, red blood cell; RBC-TI, RBC transfusion independence; RS, ring sideroblasts; s.c., subcutaneous; SF3B1, splicing factor 3b subunit 1; WHO, World Health Organization.

1. Adès L, et al. *Lancet* 2014;383:2239-2252. 2. Fenaux P, Adès L. *Blood* 2013;121:4280-4286. 3. Fenaux P, et al. *N Engl J Med* 2020;382:140-151.

Results

Table 1. Baseline erythroid biomarkers by CB response

Biomarker	Luspatercept (N = 153)			Placebo (N = 76)		
	CB (n = 89)	No CB (n = 64)	*P* value	CB (n = 16)	No CB (n = 60)	*P* value
Transfusion burden,[a] mean (SD), RBC units	n = 89 10.404 (5.96)	n = 64 11.906 (4.74)	0.08520	n = 16 12.31 (9.80)	n = 60 11.32 (4.43)	0.69734
Hemoglobin, mean (SD), g/L	n = 83 89.78 (9.78)	n = 62 87.59 (11.70)	0.23526	n = 15 87.93 (9.14)	n = 59 85.53 (9.83)	0.37900
Serum EPO, mean (SD), IU/L	n = 85 184.24 (252.44)	n = 64 248.92 (262.97)	0.13297	n = 16 87.83 (45.43)	n = 60 312.90 (478.4)	0.00066
≤ 100	n = 47 58.70 (24.04)	n = 18 51.93 (30.94)	0.41029	n = 9 51.96 (21.90)	n = 30 56.03 (22.91)	0.63644
> 100 to ≤ 200	n = 18 144.15 (24.18)	n = 21 141.01 (22.62)	0.68019	n = 7 133.9 (10.51)	n = 8 147.2 (30.66)	0.28219
> 200	n = 20 515.35 (352.01)	n = 25 481.39 (291.27)	0.73074	—	n = 22 723.4 (600.6)	—
BM EP, mean (SD), %	n = 87 31.31 (14.35)	n = 63 26.53 (12.22)	0.02975	n = 16 33.44 (16.05)	n = 59 28.89 (15.94)	0.32427
Serum ERFE, mean (SD), ng/mL	n = 80 21.36 (12.26)	n = 57 20.22 (8.62)	0.52414	n = 16 23.90 (10.80)	n = 52 22.55 (11.33)	0.66827
Serum sTfR1, mean (SD), nM	n = 82 31.45 (18.81)	n = 61 31.79 (18.57)	0.59966	n = 16 34.66 (20.22)	n = 58 30.77 (18.83)	0.49573
Reticulocyte count, mean (SD), $\times 10^9$/L	n = 75 36.75 (19.14)	n = 60 31.65 (13.30)	0.07091	n = 13 51.62 (33.64)	n = 55 35.31 (17.68)	0.11319

Data cutoff: July 1, 2019.
[a]Transfusion burden during the 16 weeks prior to randomization.
EP, erythroid precursor; ERFE, erythroferrone; SD, standard deviation; sTfR1, soluble transferrin receptor-1.

Results (cont.)

Figure 2. Reticulocyte count at baseline and during primary treatment phase (Weeks 1-24)

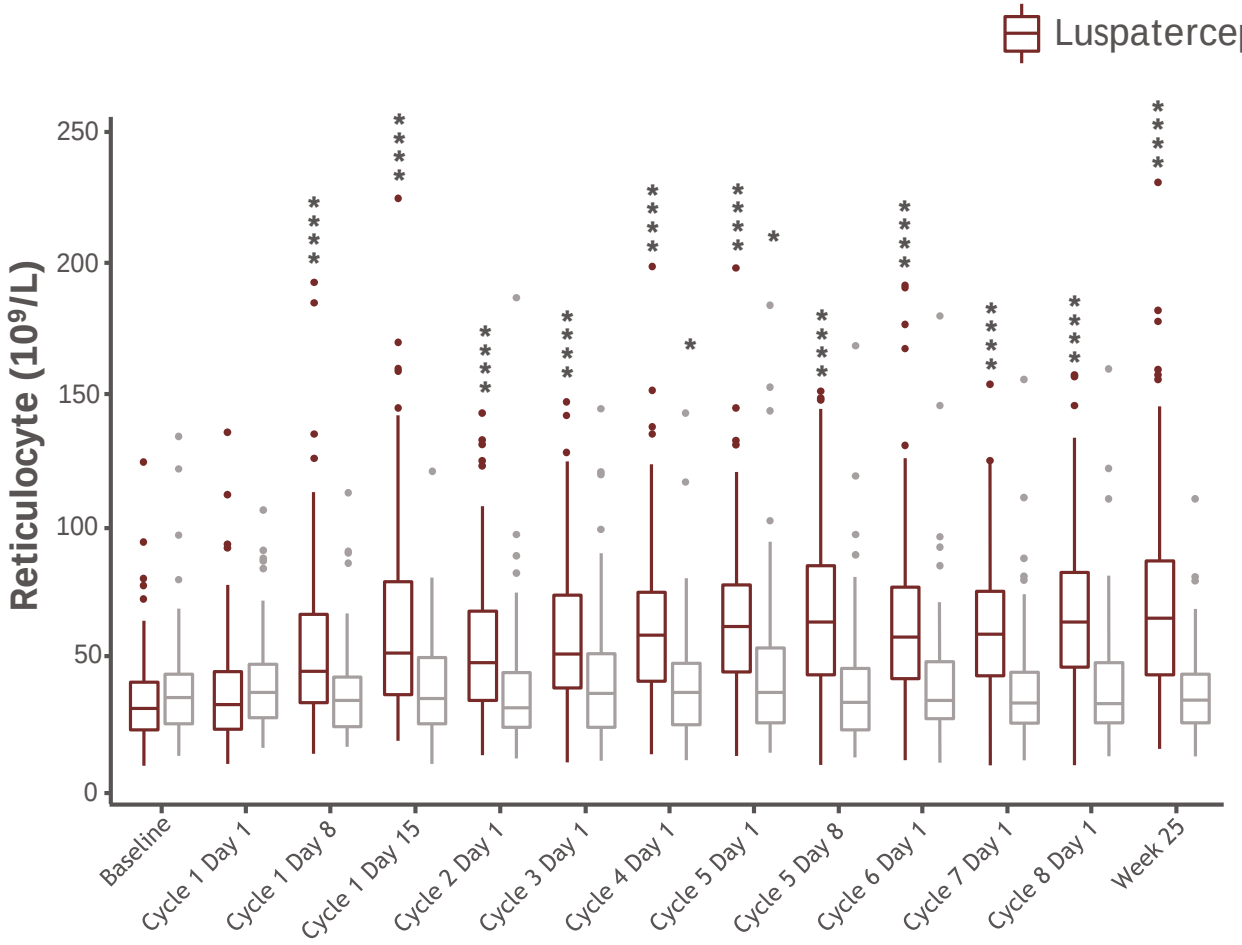
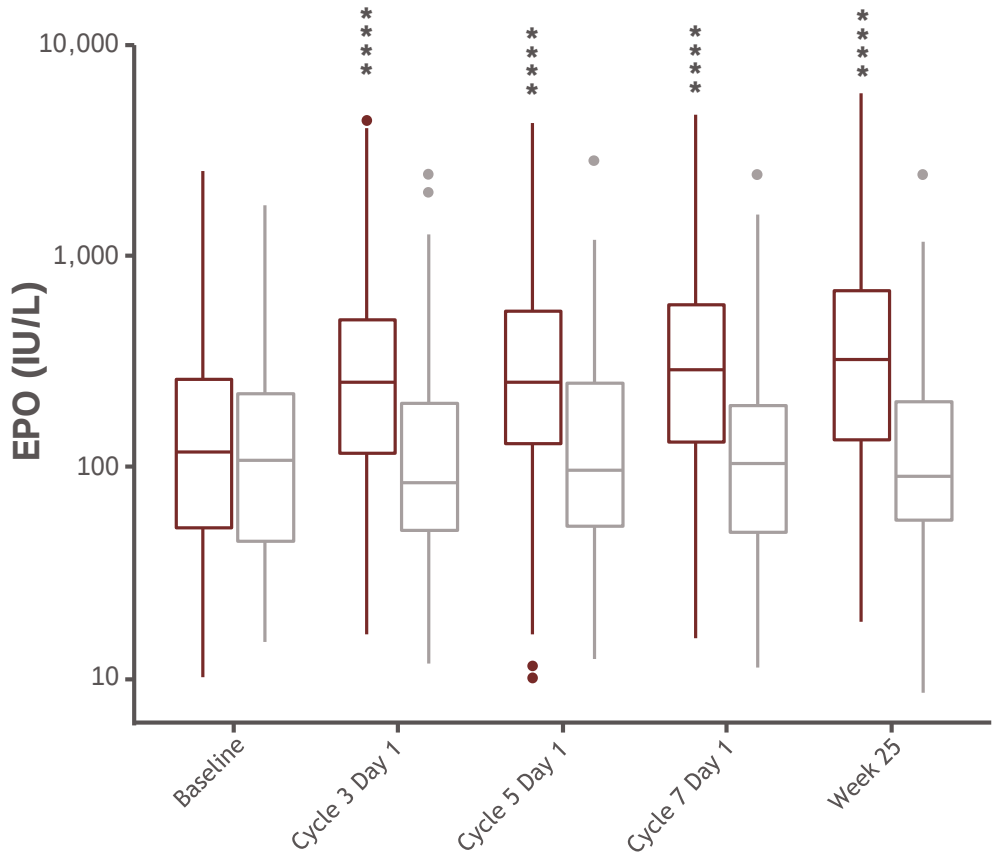


Figure 3. Serum EPO at baseline and during primary treatment phase (Weeks 1-24)



Data cutoff: July 1, 2019.
* $P < 0.05$ **** $P < 0.0001$ vs. Baseline

Results (cont.)

Table 2. Erythroid biomarkers and transfusion burden at baseline and after primary treatment phase (Weeks 1-24)

Biomarker	Luspatercept (N = 153)			Placebo (N = 76)		
	Baseline	Week 25	*P* value	Baseline	Week 25	*P* value
Serum EPO, mean (n), IU/L	220.4 (152)	662.9 (120)	< 0.0001	215.5 (74)	243.2 (64)	0.3593
Serum sTfR1, mean (n), nM	32.7 (143)	42.8 (125)	< 0.0001	31.6 (74)	23.8 (66)	< 0.0001
Serum ERFE, mean (n), ng/mL	20.9 (137)	27.0 (122)	< 0.0001	22.9 (68)	22.4 (58)	0.0431
BM EP, mean (n), %	29.3 (150)	34.3 (130)	0.0010	29.9 (75)	23.4 (66)	0.0010
Reticulocyte count, mean (n), $\times 10^9$/L	34.5 (135)	71.9 (108)	< 0.0001	38.4 (68)	37.3 (58)	0.4891
Transfusion burden,[a] mean (n), RBC units	11.0 (153)	7.2 (128)	< 0.0001	11.5 (76)	12.0 (68)	0.4438

Data cutoff: July 1, 2019.
[a]Transfusion burden during the 16 weeks prior to randomization.
EP, erythroid precursor.

Results (cont.)

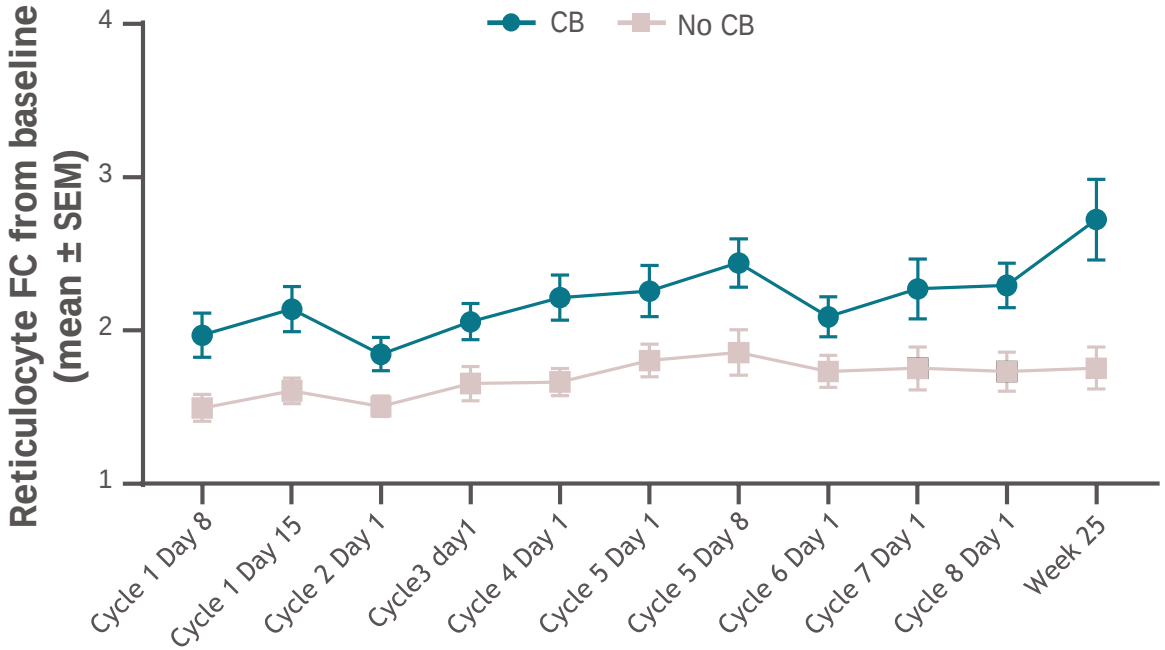
Table 3: Erythroid biomarker FC from baseline by CB (Week 25)

Biomarker	Luspatercept (N = 153)					Placebo (N = 76)				
	CB (n = 89)		No CB (n = 64)		*P* value	CB (n = 16)		No CB (n = 60)		*P* value
	Mean (SD)	n	Mean (SD)	n		Mean (SD)	n	Mean (SD)	n	
Serum EPO	2.88 (2.05)	76	4.30 (6.23)	47	0.1370	1.56 (1.50)	15	1.04 (0.68)	51	0.2138
Serum sTfR1	1.51 (0.59)	73	1.29 (0.63)	43	0.0667	0.86 (0.36)	15	0.82 (0.29)	49	0.7398
Serum ERFE	1.44 (0.69)	71	1.26 (0.73)	40	0.2154	0.90 (0.39)	14	0.99 (0.56)	39	0.5229
BM EP	2.21 (6.71)	81	1.23 (0.78)	46	0.1997	0.91 (0.36)	15	1.51 (3.21)	50	0.1971
Reticulocyte	2.72 (2.0)	57	1.75 (0.87)	40	0.0017	1.11 (0.58)	11	1.15 (0.53)	42	0.8419

Data cutoff: July 1, 2019.
FC, fold change.

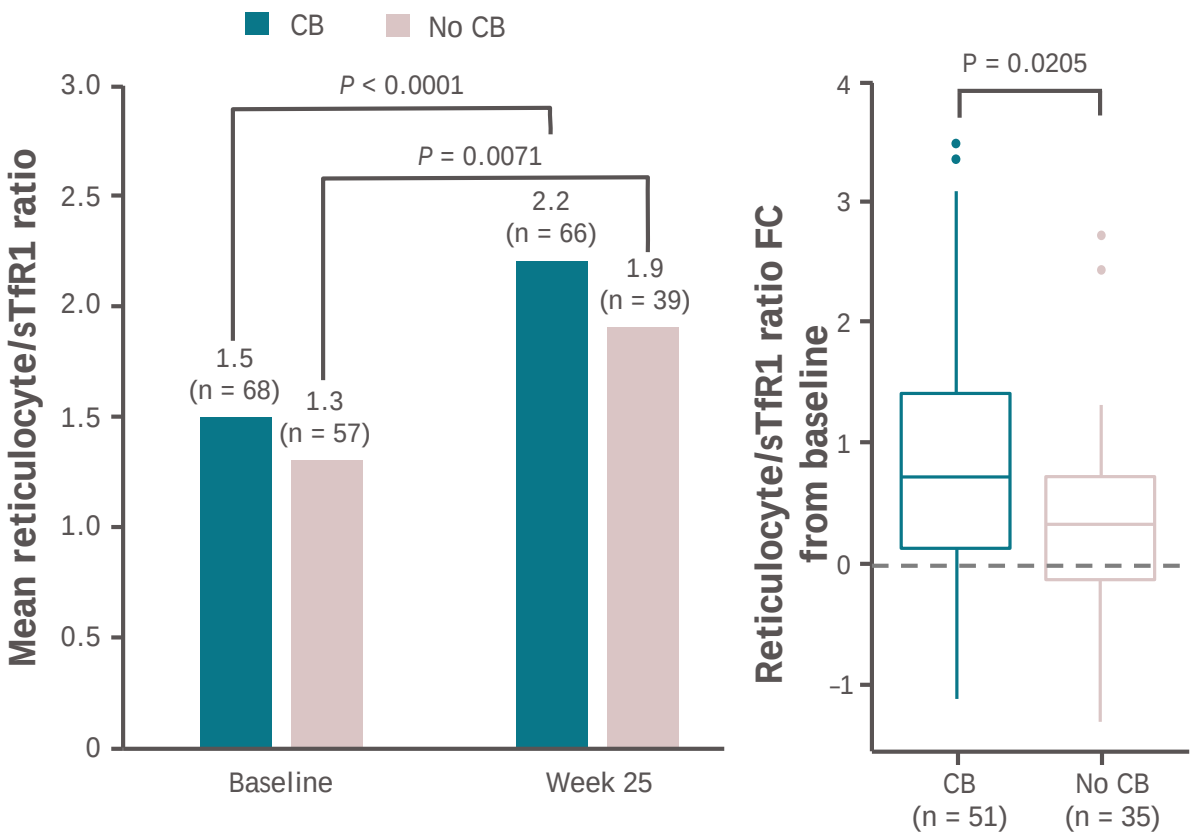
Results (cont.)

Figure 4. Reticulocyte changes in luspatercept-treated patients by achievement of CB



Mean reticulocyte FC from baseline											
	C1D8	C1D15	C2D1	C3D1	C4D1	C5D1	C5D8	C6D1	C7D1	C8D1	Week 25
CB	1.97	2.14	1.84	2.06	2.22	2.26	2.44	2.09	2.27	2.29	2.72
No CB	1.49	1.61	1.50	1.65	1.66	1.81	1.86	1.73	1.75	1.73	1.75
***P* value**	0.006	0.0024	0.0088	0.0156	0.0017	0.0254	0.0081	0.0337	0.0323	0.0046	0.0017

Figure 5. Reticulocyte/sTfR1 ratio in luspatercept-treated patients by achievement of CB



Data cutoff: July 1, 2019. * *P* < 0.05.
C, cycle; D, day; SEM, standard error of mean.

Summary

- Increases in biomarkers associated with erythropoiesis (reticulocytes, sTfR1, EP, ERFE, and EPO) were observed in patients who received luspatercept, but not placebo, in the MEDALIST trial
- In the luspatercept arm, achievement of CB (RBC-TI ≥ 8 weeks and/or mHI-E) was associated with a greater percentage of bone marrow erythroid precursor
- In the luspatercept arm, reticulocytes and EPO increased in the first 1-3 weeks of the primary treatment phase and remained elevated at Week 25
- Increased reticulocyte counts occurring in first 8-12 weeks and maintained throughout the primary treatment phase, were associated with luspatercept-mediated CB
- Luspatercept increased erythroid maturation in patients with LR-MDS with RS as evidenced by early and sustained increases in reticulocyte counts and the ratio of reticulocytes to sTfR1

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